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BRIEF REPORT

Respiratory Viral Testing and Influenza Antiviral Prescriptions During Hospitalization for Acute Respiratory Illnesses

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We examined respiratory viral testing and influenza antiviral prescriptions at a US tertiary care hospital. During the 2010–11 to 2012–13 influenza seasons, antiviral prescriptions among acute respiratory illness (ARI) hospitalizations were associated with viral testing (rate ratio = 15.0), and empiric prescriptions were rare (<1% of ARI hospitalizations).

Keywords. influenza; influenza antivirals; respiratory virus testing; acute respiratory illness hospitalizations

Influenza is associated with 100 000–600 000 hospitalizations each year [1]. When given early to patients hospitalized with influenza, ideally within 48 hours of illness onset, influenza antiviral treatment can provide clinical benefit and reduces the risk of death [2]. The Centers for Disease Control and Prevention and the Infectious Diseases Society of America recommend early, prompt antiviral treatment for persons hospitalized with confirmed or suspected influenza [3, 4]. Among those hospitalized with laboratory-confirmed influenza in the United States, approximately 80% reported receiving antiviral treatment [5]. However, little is known about influenza diagnostic testing and the relationship between treatment and testing among inpatients with suspected influenza.

METHODS

Electronic administrative records from a large (>1500 beds), academic tertiary care hospital in Connecticut were accessed for admissions (≥1 day), occurring from October 1, 2010 through April 29, 2013. Included records had admission or discharge *International Classification of Disease, Ninth Edition* (ICD-9) codes for influenza-like, acute respiratory illness (ARI); predefined as otitis media (ICD-9 codes: 381–382), acute respiratory infections (460–466), other diseases of the upper respiratory tract (470–478), pneumonia/influenza (480–488), chronic obstructive pulmonary disease (COPD)/allied conditions (490–496), other diseases of the respiratory system (510–519), or dyspnea/respiratory abnormalities (786). Influenza seasons were defined from October 1 through April 30 the following year. Hospitalizations within 21 days of a prior ARI admission were excluded.

Preexisting medical conditions that can increase the risk of influenza complications were considered present if any medical encounter due to chronic lung disease, metabolic disorders, cardiovascular disease, blood disorders and hemoglobinopathies, neuromuscular and neurologic disorders, immunocompromised conditions, chronic renal disease, or asthma was recorded during the year before admission.

Antigen-based (direct fluorescence assay [DFA]) and molecular (reverse-transcriptase polymerase chain reaction [RT-PCR]) panel assays were available for influenza testing throughout the study period with results available 2 hours to 3 days after specimen collection. Both assays detected influenza A and B, parainfluenza 1–3, human metapneumovirus, adenovirus, and respiratory syncytial virus. All tests ordered within 3 days of admission were included in analysis.

Any influenza antiviral prescriptions ordered during hospitalization were included. Prescriptions were considered empiric if ordered before a viral test was ordered, if a viral test was never ordered, or if the test came back negative for influenza or considered test-directed if ordered the same day as or after a positive influenza result.

Testing and prescription percentages were season- and age-adjusted using direct standardization with total ARI hospitalizations during the study period as the standard population. Percentages were compared using Poisson regression in SAS version 9.3 (SAS Institute, Cary, NC). Trends across influenza seasons were assessed using the Cochrane-Armitage test.

RESULTS

From October 1, 2010 through April 29, 2013, we identified 45 047 ARI hospitalizations; 27 137 (60%) occurred during influenza seasons. Tests for respiratory viruses were ordered more frequently during influenza season (data not shown), and all further results were restricted to influenza seasons. Overall, across all influenza seasons, 33% of ARI hospitalizations were tested for respiratory viruses (95% confidence interval [CI], 29–37%), and testing did not vary significantly by season ($P = .24$). Among inpatients tested, 41% were tested by DFA only, 2% by RT-PCR only, 54% by DFA and RT-PCR, and

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3% had unknown test type. Seventeen percent of tests were positive for influenza during the peak week of the 2010–11 season, 10% during 2011–12, and 30% during the 2012–13 season.

Viral testing was greatest among children under 2 years old, with 60% of ARI hospitalizations tested, compared with 46% for those 2–4 years, 27% for those 5–17 years, 25% for those 18–49 years, 30% for those 50–64 years, 31% for those 65–74 years, and 35% for those ≥ 75 years. Across seasons, testing significantly declined among children under 2 years (68%, 66%, and 50% during the 2010–11, 2011–12, and 2012–13 seasons, respectively; $P < .001$), but it increased significantly among those aged ≥ 75 years (32%, 34%, and 40% in 2010–11, 2011–12, and 2012–13 seasons, respectively; $P < .001$). Patients with underlying high-risk conditions were significantly more likely to be tested than those without (38% vs 26%, respectively; $P < .001$). Among patients with pneumonia/influenza codes at admission (5% of 27 137 hospitalizations), 69% had respiratory viral tests ordered.

Over the study period, 617 ARI hospitalizations included an antiviral prescription (2.3%; 95% CI, 2.1%–2.5%), and the only antiviral prescribed was oseltamivir. A higher percentage of adults aged ≥75 years were prescribed antivirals compared with younger inpatients (2.9% vs 1.5%; $P = .012$). Antiviral prescription was similar in those with and without high-risk conditions (1.5% vs 1.4%, respectively; $P = .40$).

Antiviral prescriptions were significantly associated with respiratory virus testing (rate ratio, 15.0; 95% CI, 8.6–26.3). Of ARI hospitalizations with laboratory-confirmed influenza, 65% were prescribed antivirals, with 99% of prescriptions dated the same day or after the diagnostic test was ordered.

Evidence for empiric prescriptions was suggested in 192 (0.7%) ARI hospitalizations and test-directed prescriptions in 411 (1.5%) ARI hospitalizations. Among those tested for respiratory viruses, 1.3% had an empiric and 4.6% had a test-directed prescription for influenza antivirals. The percentage of inpatients with an empiric prescription was highest among those with an admission or discharge code specific for influenza (12.5%; Supplemental Table 1). The percentage of inpatients with an antiviral prescription, either empiric or test-directed, increased during the influenza season, peaking at 18% of all ARI hospitalizations during the 2012–13 season (Figure 1).

DISCUSSION

During the 2010–11 to 2012–13 influenza seasons, testing for influenza and other respiratory viruses was not common among patients hospitalized with an ICD-9 code for ARI at a large, academic hospital in the United States. Testing was greatest among inpatients at high risk of developing influenza complications, including young children and those with underlying medical conditions. Although the percentage tested was lower than in young children, older adults were tested significantly more during the 2012–13 season, possibly reflecting a more severe influenza season [6].

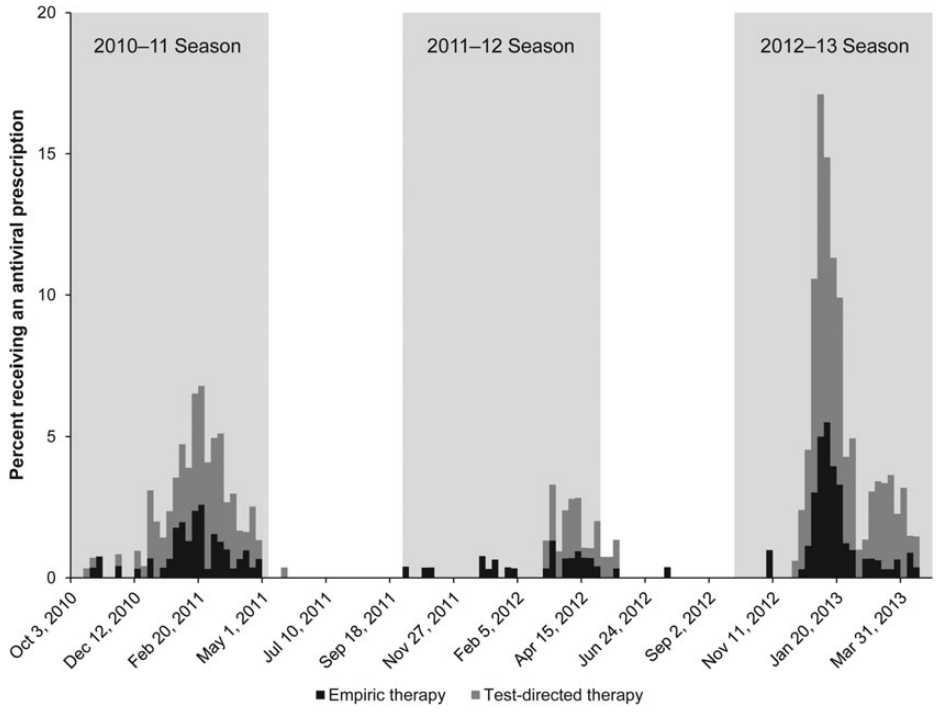

Figure 1. Percentage of patients receiving an influenza antiviral prescription, by week, among patients hospitalized with acute respiratory illness at a large, tertiary care hospital in Connecticut, October 2010–April 2013.

The percentage of hospitalized patients with ARI receiving an antiviral prescription was low and strongly associated with testing, as seen in other studies [7]. Although the majority (65%) of inpatients with laboratory-confirmed influenza was prescribed antiviral medication, the dependence on test results led to low rates of empiric prescription. Not surprisingly, the frequency of empiric prescriptions increased during the influenza season, proportionate to increases in testing and test-directed prescriptions, but without eclipsing test-directed prescriptions, as might be expected at the peak of influenza activity.

Influenza testing impacts clinical judgment and treatment decisions; however, variability in sensitivity and timeliness of diagnostic tests may result in missed opportunities for, or delays in, influenza treatment. Because neuraminidase inhibitors are most effective when given as soon as possible after symptom onset [8, 9], current guidance recommends that the decision to start treatment in hospitalized patients with suspected influenza should not wait for confirmatory test results [4], and empiric therapy is often needed to avoid treatment delays [10]. In our study, physicians had access to both a quick, although less sensitive, test (DFA) and a sensitive PCR diagnostic assay, and therefore treatment was mostly test-directed. In addition, although we recognize that influenza accounted for a fraction of ARI hospitalizations, even when influenza or pneumonia was specifically mentioned in admission codes, only 3.4% of inpatients were ordered an antiviral prescription empirically, suggesting that opportunities for influenza treatment may have been missed.

Few studies have evaluated the cost effectiveness of various test-and-treat strategies among US inpatients to help inform the best use of sensitive, yet expensive, molecular assays in aiding influenza treatment decisions. In Hong Kong, empiric treatment was found to be the most cost-effective approach among inpatients in most situations when influenza prevalence was high [11]. However, in a US setting, RT-PCR confirmation was the most cost-effective strategy when intravenous peramivir was required [12]. Although cost is an important consideration, the turnaround time for sensitive PCR assays needs to be considered as well. One study suggested that rapid multiplex PCR-based platforms, with results in 1–2 hours, may be a suitable solution to clinicians who prefer to confirm influenza before prescribing antiviral medications, if the test-associated costs can be minimized [13].

This analysis has several limitations. First, data were available from a single hospital site with limited generalizability, because other hospitals may use different diagnostic tests and treatment protocols. Second, data on symptom onset, which may have influenced viral testing and antiviral prescriptions, were not available. Of note, treatment is recommended for any person with suspected or confirmed influenza requiring hospitalization, even if started >48 hours after symptom onset [4].

CONCLUSIONS

In our study, almost all influenza antiviral prescriptions were test-directed. Although influenza diagnostics lend support to clinical decisions, reliance on insensitive tests or assays with long turnaround times could result in missed opportunities for treatment. Healthcare providers are encouraged to start influenza antiviral treatment as soon as possible for patients hospitalized with suspected influenza, often on an empiric basis, especially during periods of high influenza prevalence. Studies that lend insight into methods to optimally use test-directed or empiric treatment strategies may improve care of patients hospitalized with influenza.

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Supplementary Material

Supplementary material is available online at Open Forum Infectious Diseases (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

References

1. Reed C, Chaves SS, Daily Kirley P, et al. Estimating influenza disease burden from population-based surveillance data in the United States. PLoS One **2015**; 10: e0118369.
2. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med **2014**; 2:395–404.
3. Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children–diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis **2009**; 48:1003–32.
4. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **2011**; 60:1–24.
5. Garg S, Chaves SS, Perez A, et al. Reduced influenza antiviral treatment among children and adults hospitalized with laboratory-confirmed influenza infection in the year after the 2009 pandemic. Clin Infect Dis **2012**; 55: e18–21.
6. Centers for Disease Control and Prevention (CDC). Influenza activity–United States, 2012-13 season and composition of the 2013-14 influenza vaccine. MMWR Morb Mortal Wkly Rep **2013**; 62:473–9.
7. Lindegren ML, Griffin MR, Williams JV, et al. Antiviral treatment among older adults hospitalized with influenza, 2006-2012. PLoS One **2015**; 10:e0121952.
8. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. J Antimicrob Chemother **2003**; 51:123–9.
9. Heinonen S, Silvennoinen H, Lehtinen P, et al. Early oseltamivir treatment of influenza in children 1–3 years of age: a randomized controlled trial. Clin Infect Dis **2010**; 51:887–94.
10. Centers for Disease Control and Prevention. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season. Available at: http://www.cdc.gov/H1N1flu/recommendations.htm. Accessed 13 October 2015.
11. You JH, Chan ES, Leung MY, et al. A cost-effectiveness analysis of "test" versus "treat" patients hospitalized with suspected influenza in Hong Kong. PLoS One **2012**; 7:e33123.
12. Lee BY, Tai JH, Bailey RR, et al. Economic model for emergency use authorization of intravenous peramivir. Am J Manag Care **2011**; 17:e1–9.
13. Nelson RE, Stockmann C, Hersh AL, et al. Economic analysis of rapid and sensitive polymerase chain reaction testing in the emergency department for influenza infections in children. Pediatr Infect Dis J **2015**; 34:577–82.